IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION This document relates to: *All Actions*	No. 19-md-2875-RBK Honorable Robert Kugler Special Master Thomas Vanaskie

DECLARATION OF MAHYAR ETMINAN PHARMD, MSC

1. This Declaration is submitted as my direct testimony for the Daubert hearing, and is based on my personal knowledge.

2. Defendants state on page 10 of their reply brief: "He also disregarded the valsartan-specific studies, Gomm and Pottegard, due to 'inadequate cancer latency or the time required for the cancer process to complete and lead to symptomatic disease. Report at 31." The partial quote is cited from the summary section of my report, and does not apply to my evaluation of Gomm or Pottegard. That partial quote is taken from a part of my report that discusses dietary studies. That part of my report references **Figure 1**, which is on page 30 of my report. Neither Pottegard nor Gomm appear in Figure 1 of my report.

3. Contrary to the inaccurate characterization of my report by the Defendants, I discuss the reasons why I gave little weight to Gomm and Pottegard in the first paragraph on page 31 of my report. I first noted that, "To date, two epidemiologic studies have attempted to quantify the risk of cancer with valsartan formulations that contain excessive amounts of NDMA [64, 65]." Citation 64 of my report is Pottegard. Citation 65 of my report is Gomm. The report further states, "The results of the studies were inconclusive as they were subject to a number of limitations, mainly a short duration of follow up but most importantly the inability to precisely quantify the

amount of NDMA in the valsartan formulations used in both studies." I elaborate within the body of my report as to how those studies attempted to classify exposure, for example, Gomm and Pottegard only required subjects to have filled a single prescription of valsartan to be included in the cohort of people assumed to have possibly consumed valsartan contaminated with NDMA.

4. Some of the most significant exposure classification limitations of Pottegard are set forth on page 25 of my report, which I've included below:

- All subjects who possibly ingested NDMA contaminated valsartan were grouped together as the authors looked at the cumulative dose of valsartan (mg of the pill) as the unit of analysis and not the cumulative amount of NDMA (which is the actual exposure of interest). This limitation will undoubtably lead to misclassification of exposure as the varying amounts of NDMA from different batches and manufacturers is not accounted for using this approach since the study's hypothesis was that higher doses of NDMA will cause cancer and not higher doses of valsartan per se. Due to this limitation, one could reasonably anticipate that the study would not produce statistically significant harmful effect of NDMA with cancer and would have missed a possible risk of cancer with valsartan contaminated NDMA.
- The authors did not account for the possibility that a patient could be switched from a non-NDMA containing valsartan to an NDMA containing valsartan during the follow-up period.
- Daily doses of valsartan (80mg, 160mg, 320mg) were utilized in an attempt to quantify NDMA exposure and stratify the results based on cumulative NDMA exposure. The notion that the level of NDMA contamination will increase as the milligram of the valsartan pill increases, is only true when all pills are made from the same contaminated batch of active pharmaceutical ingredients (API). What has been discovered since the publication of Pottegard[64] is that batches of API can vary by orders of magnitude on their level of NDMA contamination. As such, an 80mg tablet of valsartan can have substantially higher levels of NDMA in it than a 320mg tablet. These discrepancies can lead to exposure misclassification, resulting in false negatives.

5. My discussion of Gomm appears on page 26 of my report. Even though Gomm detected a statistically significant increased risk of liver cancer, I gave Gomm little weight. On page 26 of my report I discuss how Gomm exposure classifications suffer similar major limitations as with Pottegard:

- Similar to the Pottegard[64] study, the study by Gomm[65] could not specifically identify the true NDMA levels of the various valsartan batches, and the dose-response analysis only

looked at cumulative dose of valsartan per se and not the cumulative NDMA content in the valsartan formulations (mg of pill vs. ng of NDMA in pill).

6. Finally, both studies share similar major limitations in that the cohorts assumed to have taken valsartan that was not contaminated with NDMA likely included people who took valsartan that was contaminated with NDMA. I addressed this numerous times in my deposition (Etminan Depo Tr. Vol I at 267:18-20, 268:10-15, 269:13-15, 270:22-24, 271:12-19; Etminan Depo Tr. Vol II at 20:18-19).

I certify under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on
Date: Feb 24, 2022

Mahyar Etminan PharmD, MSC

EXHIBIT A

of impurity, right?

A They're not -- I disagree. They're not -- they're not quantifying the NDMA valsartan. They are only looking at valsartan tablets and doses.

Q The exposure that they're evaluating is -- so the title of the Pottegard study is "Use of N-nitrosodimethylamine (NDMA) Contaminated Valsartan Products and Risk of Cancer: Danish Nationwide Cohort Study," right?

A That -- that is the title, but if you read the study -- the exposure that we're here today to talk about is NDMA and its risk of cancer, and so the study should address the amount of NDMA in valsartan and its risk with cancer. What it does, though, is look at valsartan tablets that have some NDMA in it, in them, we don't know how much.

And with respect to Pottegard, we -- we are not even sure if the -- the control valsartan group didn't have NDMA in those formulations.

So there is definitely measurement error going on in quantifying -- appropriately quantifying NDMA in valsartan along with other limitations.

Q Why do you say that there's definitely

measurement error?

A Because NDMA levels vary in different batches or different types of valsartan. But there are many different generic valsartan products, and they may have different levels of NDMA in them. So higher levels may put somebody at a higher risk of cancer, and this study did not look at that, which I think is an important distinct that should be looked at.

And also because the study was done early on, it turns out that some of the control group, which they -- they thought did not have NDMA in them probably did have NDMA in them as well. So there is again an error in measurement between the two groups. So that is -- that is the limitation of the, you know, measurement error portion of this study.

Q Okay. So am I understanding right, they would have to know the amount of NDMA that each of the subjects was actually exposed to to evaluate whether there actually is a risk of these cancers, from that literature?

A They would have to -- they would have to categorize -- have had to categorize the different levels of -- hello?

MR. GALLAGHER: I can hear you. Does somebody else need to mute, maybe?

THE WITNESS: Yeah, there's an echo.

They should have -- maybe they couldn't, but the -- the right thing to do is to categorize different NDMA levels in these valsartan tablets and categorize them to say: High, medium and low dose. And then follow patients for more than the amount of time, I think it's three years, I believe, that they did, to make sure that they are at risk of developing cancer.

And then also make sure that the control group does not have any NDMA in those -- in those batches. And they can also make sure there's no switching going on, because, again, patients take these drugs from their pharmacy. And they don't really specify which generic formulation they get. So there could be switching between patients, and they could be switching between the doses of NDMA over time. So all of those limitations I think probably led to the negative results.

BY MR. GALLAGHER:

Q Okay. You do agree with me that the

Pottegard study reports a negative result in terms of any association between exposure to NDMA as an impurity in valsartan and --

A Well, again, negative results with the caveat of a number of limitations.

Q Okay. And among those -- among those limitations that you've identified is the people conducting the study would need to somehow quantify the amount of NDMA to which the subjects were actually exposed in order to evaluate that potential association of exposure to NDMA as an impurity of valsartan with cancer?

A Right. I make sure that those -- those patients are taking these higher levels of NDMA for at least a specific period of time to allow the cancer process to sort of form and be diagnosed.

You know, if somebody takes the drug for three months and then leaves the study, that -- that is not a good follow up for this study. You need long follow up. You need minimal switching. You need specific NDMA dosing information for the subjects, and you need to make sure that the control group are all clean valsartan users, and there's no NDMA in them as well.

Q Okay. Moving on to the Gomm study, do

you have that now, Exhibit 27, I believe?

A Yes.

Q And you're addressing the Gomm study on Page 26 of your report. From your perspective, does the Gomm study, you know, essentially have, from your perspective, the same limitations as we just discussed for the Pottegard study?

A Yes, I would again --

MR. NIGH: Hold on. Hold on. Let me object. Form objection.

You can answer, Dr. Etminan.

THE WITNESS: Yes. Again, just like Pottegard, there's no specification of the NDMA content in the valsartan users, and I think they actually say possible or probable contamination. So there's a feeling of uncertainty as to, you know, whether, say, for example, the control group had any NDMA or did not have any NDMA. There's no discussion of what if people switch between the, you know, different doses which could have had different NDMA levels.

And then there is the problem of only a three-year follow up, which for a cancer is quite inadequate. And there's also some

in valsartan-containing medications, what we need to consider is the extent to which individual consumption of NDMA and NDEA increase due to the presence of those compounds in the drugs, right?

MR. NIGH: Form objection.

THE WITNESS: I mean, if you want to do a perfect study, yes, that's -- that's what needs to be done.

BY MR. TRISCHLER:

Q And in assessing carcinogenicity of any compound, you agree that dose and duration of exposure are always important, right?

A Generally speaking, yes.

Q Right. Well, in fact, yesterday, we discussed the Pottegard and Gomm studies. Do you remember that?

A Yes.

Q And one of the things I remember from your testimony yesterday was that you were critical of those studies because the amount of NDMA exposure was not specified in the controls. Do you recall telling us that?

A Yes.

Q And you told us that, you know, for that -- in that study, you would have liked to have